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THE SKIN, ORGAN OF DISCOVERY: YESTERDAY, TODAY, AND TOMORROW*

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THE invitation to deliver the Howard Fox Memorial Lecture does me great honor. Together with George MacKee, Fred Wise, Sigmund Pollitzer, and many other Fellows active in this section, Howard Fox helped to shape dermatology in the United States. Fox was a conscientious, careful, and conservative man who was not always fond of me, of what I represented. In retrospect, I realize that he was often right about my attitudes and conduct. Fox was fairminded and generous. He never spoke or acted against me in a personal way, and I am grateful for this first opportunity publicly to proclaim my respect for the brilliant leader and distinguished gentleman who was one of my predecessors in the chair of

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dermatology and syphilology at New York University, and who dedicated his life to our specialty.

Most, if not all of us here have dedicated ourselves to dermatology, and we know that it is a specialty extraordinarily rich in challenges and opportunities. More than 50 years as a dermatologist have convinced me that no other "organ specialty" surpasses ours in scope, variety, or opportunities. Organ specialties are not limited by modalities such as surgery or radiology, but employ any and all modalities on the organ with which they are concerned.

Among dermatology's great objectives is to decrease suffering and disability caused by skin diseases—diseases which constitute a large fraction of general medical practice (one seventh to one tenth, according to the best modern estimates). And, according to the latest accurate figures on prevalence among people one to 74 years of age in the United States, an estimated 60.6 million have one or more skin conditions requiring medical attention.[1] This objective is so obvious that it needs no further emphasis.

This evening I want to speak about another set of opportunities and challenges which I hold to be as important as the obvious ones I have mentioned. These are to utilize the skin, its diseases, and its reactions to discover fundamental phenomena and laws that have wide applicability throughout medicine, biology, and science.

Let us think back to about the turn of the century. I shall remind you of some of the instruments and techniques which were unavailable then and which we today take for granted. My list will be long and its very length impressive. There were no x rays, no electrocardiograms, no encephalograms, few endoscopes of any kind, certainly no fibre optics, no electrophoretic patterns, no immunoglobulins to separate, no immunofluorescence, no radioisotopic scans, no cardiac catheterizations, no karyotyping, no T-cell and B-cell forms and functions to differentiate, no serologic tests (the Neisser, Bruck, and Wassermann publication appeared in 1906), no darkfield examinations, few blood chemistries, no electron microscopes, and no internal biopsies—biopsies could not be made of liver, lung, kidneys, gut, or other viscera. In short, most currently available methods to examine the internal organs were lacking. Nor could physicians examine the body fluids or the body as a whole as we can today. It is, therefore, no exaggeration to say that the skin was the only human organ that could be examined scientifically, repeatedly, and safely while it was still alive

TABLE I. SOME DERMATOLOGIC CONTRIBUTIONS IN ONCOLOGY

1775	First proved cause of human cancer (Percival Pott—chimney sweeps')
1887	First proved chemical cause of cancer (Jonathan Hutchinson—arsenical skin cancers)
1890	First Precancerosis (Dubreuilh—Hutchinson)
1894	First recognition that light and elements caused cancers (Unna—farmers' and sailors' skin)
1916	First experimental cancers (Yamagiva and Itchikawa—tar in mice)
1921	First isolation carcinogenic fraction of tar (Bloch and Dreifuss)
1932	First transmission virus skin cancer (Shope—papilloma)
1968) 1970)	First U. V. damaged human DNA and its faulty repair demonstrated as carcinogenic (Cleaver—urticaria pigmentosa-endonuclease)

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and in place. The human skin's gross clinical changes and many of its histopathologic alterations, its microflora and chemical composition, its secretions, its immunologic and other reactions, and many of its normal and pathologic changes and functions were within easy and safe reach before the 20th century.

It is, therefore, neither to be wondered at nor to be boasted about that until quite recent times a substantial portion of the fundamental discoveries of medicine was derived from studies of the skin. No studies of any other living organ, no investigators in any other specialty, had an equal opportunity to make fundamental discoveries. The old-time dermatologists and syphilologists had a head start because of the accessibility of their organ and were, therefore, most likely to contribute new methods and knowledge. These advances could later be applied to research and clinical practice in many fields other than dermatology.

When I began to search out the fundamental contributions made through studies of the skin, I was amazed at their number and variety.[2] I must be selective and cannot attempt to be encyclopedic.

In oncology (see Table I) the first proved cause of human cancer,

TABLE II. SOME DERMATOLOGIC CONTRIBUTIONS IN MICROBIOLOGY

1687	First recognition of living agent causing disease (Bonomo—scabies mite)
1839	First recognition of microorganism causing disease (Schoenlein—favus)
1879	First V.D. microorganism (Neisser—gonococcus)
1884	First TBC microorganism (Koch—bacillus from lupus vulgaris)
1905	Discovery of spirochete of syphilis (Schaudinn and Hoffman)
1907	First production of human tumor with ultrafiltrable material (Ciuffo—molluscum contagiosum)

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discovered by Sir Percival Pott in 1775, was the coal soot that remained in the scrotal skin folds of "climbing boys" (chimney sweeps). The first proved simple chemical cause of cancer was arsenic, which Sir Jonathan Hutchinson in 1887 showed caused skin cancer. The first precancerosis was described by Dubreuilh (1890) and by Hutchinson: the pigmented skin lesion now called lentigo maligna. Paul Gerson Unna in 1894 first recognized that exposure of the skin to light and to the elements causes precancers and cancers in what he called farmers' and sailors' skin, Landsmans und Seemans Haut. The first experimental cancers were produced by tar in the skin of mice by Itchikawa and Yamagiva in 1916. Shortly after that (1921), Bruno Bloch and Dreifuss identified the skin carcinogenic fraction in coal-tar distillates. This was followed by the isolation of chemically pure carcinogens. The first viral skin cancers in mammals were Shope's malignant skin papillomas in rabbits (1932). And the first defect in repair of ultraviolet-ray-damaged human DNA leading to cancer was relatively recently demonstrated by James Cleaver (1968), and further studied by John Epstein and William Reed and by Tan and Stoughton in the skin of patients with xeroderma pigmentosum.

Turning to microbiology (see Table II),[2] the first living agent identified as a cause of disease was the scabies mite, a discovery many historians credit to Bonomo in 1687. The female sarcoptes is large enough to be

TABLE III. SOME DERMATOLOGIC CONTRIBUTIONS IN IMMUNOBIOLOGY

1796	Introduction of specific prophylaxis through skin vaccination (Jenner)
1895	First patch test for delayed hypersensitivity (J. Jadassohn)
1906	First serologic tests for syphilis (Neisser, Wassermann, and Bruck)
1907	First toxin antitoxin-toxoid tests—diphtheria (Schick)
1921	First passive transfer urticarial hypersensitivity (Prausnitz-Kuestner Reagin—gamma E)
1925	First specific skin test V.D. (Lymphogranuloma venereum—Frei)
1928	First specific skin sensitization simple chemicals (Frei, Sulzberger, Jadassohn, Mayer, et al.)
1940's	First cell mediated hypersensitivity transfer (Landsteiner, Chase, Lawrence—transfer factor)
1929 through 1940s	First productions of immune tolerance (Chase, Sulzberger, Medawar, Burnet)

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visible to the naked eye, and not until many years later was a pathogenic organism not visible to the naked eye, i.e., a microorganism, shown to cause human disease. Again, this was in a skin disease—or rather in disease of a skin appendage, namely, the hair. Shoenlein of Zürich discovered the fungus that caused favus, *Achorion Schoenleini* (1839).

The first microorganism proved to cause a venereal disease was the gonococcus, discovered by the great Breslau dermatologist and syphilologist Albert Neisser (1879). And the tubercle bacillus, which was first isolated by Koch (1884), came from a patient with lupus vulgaris—not from the lungs, not from tuberculosis of any other organ, but from cutaneous tuberculosis.

Schaudinn and Ehrich Hoffman, a dermatologist (1905), discovered the spirochete of syphilis, the *Treponema pallidum*. Ciuffo (1907) demonstrated the first ultrafilterable infectious material to produce a human disease in transmission of a skin disease, molluscum contagiosum.

In immunobiology (Table III),[2] it is probable that the skin has led to more discoveries than in any other field. Because he had noted the scars of cow pox on the skin of the hands of milkmaids and observed their subsequent immunity to smallpox, Jenner introduced skin vaccination (1796), an immunologic prophylactic procedure which has for practical purposes eliminated smallpox from the world.

Josef Jadassohn introduced the first systematic use and accurate interpretation of the patch test in 1895, 11 years before von Pirquet (1906) coined the word "allergy."

The first practical serologic test for syphilis was based on the complement-fixation reaction discovered by Bordet and Gengou in France and applied to the diagnosis of syphilis by Neisser, together with Wassermann and Bruck (1906). They first produced a clinically specific and sensitive serologic test for syphilis, now known as the Wassermann test.

Bela Schick could neither have titrated his antitoxin neutralizations of diphtheria toxin nor developed his magnificent diagnostic and prophylactic procedures without using the skin as test tissue. The experiment which finally led to the discovery of immunoglobulin E was the Prausnitz-Kuestner procedure carried out in the human skin with atopic reagins (1921). The first diagnostic skin test for venereal diseases was that by Wilhelm Frei of Breslau in lymphogranuloma venereum (1925).

The classic sensitization experiments of Landsteiner and Jacobs using simple chemicals followed those by dermatologists in both guinea pig and human skin (1928) (Wilhelm Frei, neoarsphenamin; Mabel Silverberg, mesothan; R.L. Mayer, paraphenylendiamine; W. Jadassohn, phenylhydrazine; etc.).

When I first met Karl Landsteiner in 1929 he did not believe that simple chemicals could sensitize without the small molecule of the hapten first being conjugated to a large molecule *in vitro,* and told me most emphatically that what Frei and I had published about skin sensitizations with neoarsphenamin alone was impossible, was nonsense.

The first transfers of delayed type hypersensitivity by white cells could not have been demonstrated without skin tests (Chase, Lawrence), and the earliest demonstrations of what is now called immune tolerance were the lasting immunity or refractoriness to skin sensitization by simple chemicals produced by Merrill Chase and me (1929).

Time makes it impossible to recount innumerable contributions by skin studies to other branches of medicine and science[2] (for example, to endo-

Fig. 1. The dermatologic clinic of the University of Zürich. The author lived for almost three years in one of the rooms with gabled windows on the top floor, together with other assistants of Professor Bruno Bloch. Reproduced by permission from Sulzberger, M. B.: Strong swimmers on a full sea, Part II. *Int. J. Dermatol. 15*:615, 1976.

crinology, to occupational medicine, to the study of chemical mediators [beginning with Sir Thomas Lewis' triple response of the skin to histamine]; and to the recognition of genetic diseases). It is apparent that new knowledge concerning the biologic effects of physical agents such as cold, heat, light, and ionizing radiation should come from observations of changes in that large organ which is most exposed to their effects, the human skin. Thus, the first biologic effects of radium were discovered by chance in 1901 when Becquerel burned his skin by carrying in his trouser pocket a bit of radium that his friends, the Curies, had given him. It was the great French dermatologist Besnier who turned Becquerel's pocket inside out and recognized that his skin burn was due to radium.

In physical medicine it is particularly noteworthy that Finsen of Copenhagen was the first to use systematic phototherapy upon the skin, and that what is today popularly called cryotherapy was employed on skin lesions as early as 1907 by William Allen Pusey, the distinguished Chicago dermatologist. I must not omit the role the skin has played in elucidating the action of heat and cold, including the phenomena of blood shunting and of sweat reaction to acetylcholine.

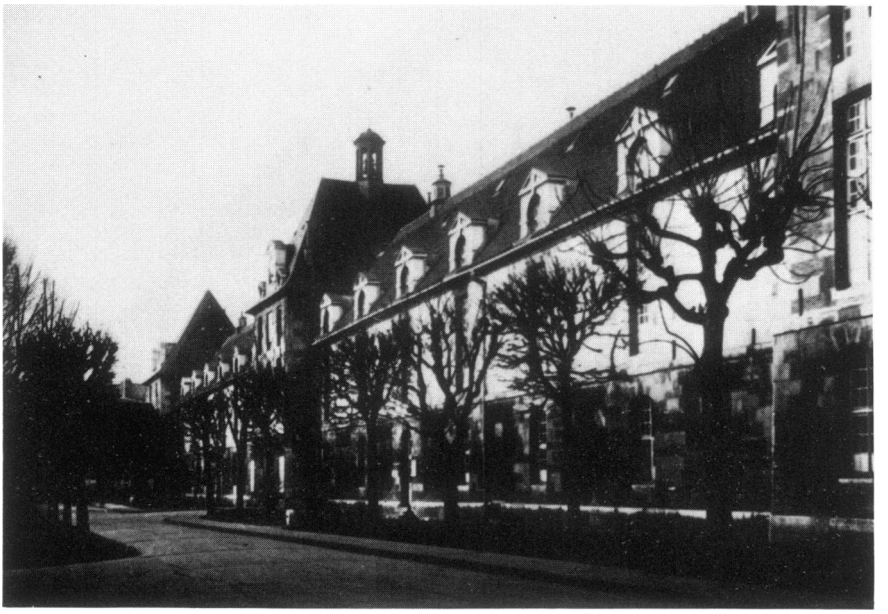

Fig. 2. One facade of one of the group of buildings of the great Hôpital Saint Louis of the University of Paris.

Do these selected examples of scientific advances wrested from studies of the skin fully explain how and why European dermatologists of yore got their prestige, funds, facilities, space, and research institutes? I do not believe so. I believe that dermatologists got their power and their lavish governmental support less because of their research achievements than because of their countries' immediate practical needs. The availability of experts able to make accurate diagnoses of skin diseases without modern laboratory aids which did not then exist was of utmost importance, particularly in the European countries then almost constantly at war. Some of a country's military effectiveness, wealth, and public health depended to a not negligible extent upon having experts who could recognize what was syphilis and what was not syphilis; what was leprosy and what was not leprosy; what was malignant, what benign; what was transmissible and due to fungi, lice, or mites and what was not; which disease was hereditary, which was not; which patient would get worse, which would remain unchanged, and which would recover; and so forth. And dermatologists, with their trained eyes, expertness in sharply focussed history taking,

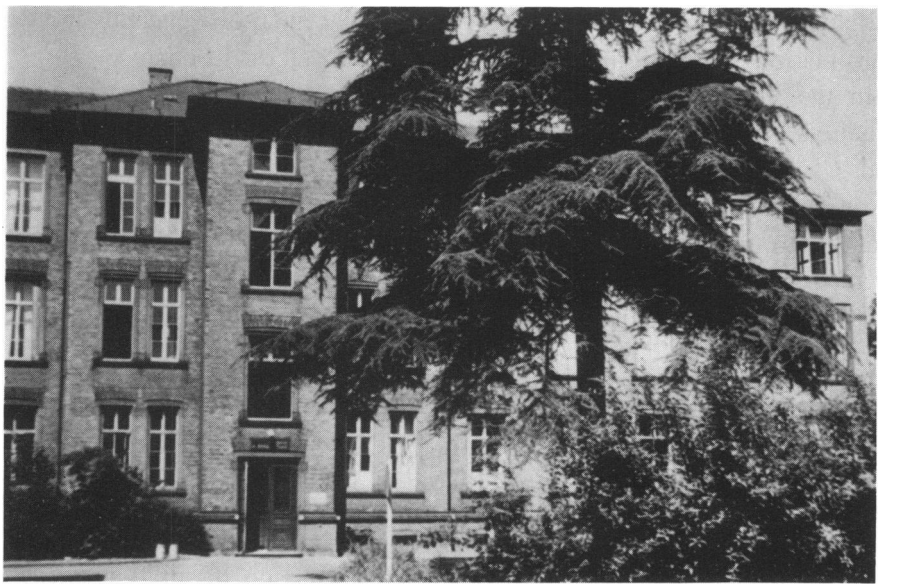

Fig. 3. One of the five buildings of the dermatologic university clinic of Frankfurt (Herxheimer's original clinic).

experience, and clinical acumen, were the only ones who made these crucial differential diagnoses with a batting average of well over .500. And if the dermatologists seemed to be magicians in their diagnoses, they seemed almost equally so in their therapies. Treatment of skin diseases could not employ antibiotics, antihistamines, sulfonamides, and such systemic "wonder drugs," but consisted in large part of shake lotions, ointments, pastes, plasters, baths, poultices, and compresses. These topical agents sometimes contained upward of five distinct active ingredients, carefully selected, skillfully compounded, correctly and scrupulously applied and removed.

Naturally, the governments—and universities were state supported—gave dermatologists the tools they required and the institutions they needed to carry out their diagnoses and therapy. Huge buildings and groups of buildings, well-equipped, staffed, funded, and devoted to dermatology and syphilology, dotted Europe from the Atlantic to beyond the Urals (Figures 1,2,3).

In the United Kingdom, London's St. John's Hospital for Skin and Venereal Diseases also received the space and equipment it required,

perhaps in part because it stood in the very center of venereal disease transmission, a step from Piccadilly Circus and Leicester Square.

In the United States before 1900 only one institute for dermatology acquired its own separate, well-equipped building—the New York Skin and Cancer Unit, founded in 1882. The acquisition of funds for this institution's construction and maintenance may have been due in some measure to the courage of its board of directors in using the word cancer in its official name—to become the first hospital in our country that dared to proclaim that it treated cancer, a word so dreaded that it was taboo in most families.

It seems likely to me that dermatologists often got cash and credit more from funds for venereal disease, cancer, and for increasing military and industrial effectiveness than because they knew how to diagnose and treat the common skin diseases of ordinary private patients. There may be a lesson here for dermatologic research today.

Dermatologic research contributed a great fraction of all fundamental discoveries before the existence of the countless modern instruments and techniques to study internal organs. And, inevitably, as modern techniques and instruments became available, more discoveries would be made through studies of organs other than the skin. A natural question is whether increased ability to examine noncutaneous tissues and fluids has decreased dermatology's ability to contribute to fundamental knowledge. All the evidence convinces me that this is not so. The ratio of discoveries made through studies of the skin to discoveries made through investigations of other organs has decreased, and dermatologists today use discoveries made by others much more than they did formerly. Our specialty could not exist without using discoveries from every provenance. But the greatest acclaim goes to those who supply new knowledge and new methods of fundamental usefulness far beyond the organ on which the studies were done.

Jonathan Hutchinson's statement remains as true now as when he said, "If I'm not mistaken, the time is not distant when diseases of the skin, instead of being esteemed an unimportant if not repulsive specialty, will be regarded as affording unequalled opportunities for the study of morbid processes."

Here are a few examples where the skin still affords unequalled opportunities for fundamental discoveries which extend beyond skin diseases and promise wide applicability in medicine and science.

Medawar, Burnet, Billingham, Brent, and others investigated what is

now called immune tolerance. This was demonstrated by Sir Peter Medawar and his group, mainly through studies on how to prevent skin-homograft rejection in pure strains of mice. They demonstrated that pure strains of brown or black-haired mice would not reject transplants from white-haired mice if they had been exposed intrauterine to white-haired mouse material—and vice versa. That fundamental, Nobel Prize-winning work could not have been accomplished as easily, readily, or early had it not used skin color (or, rather, hair color) as a marker.

In tumor immunology the most promising results have been in skin tumors, particularly in melanomas, and it should be recalled that the cardinal first observation in the immunologic cure of tumors was the spontaneous or stimulated destruction of skin pigment and of the mole in the halo nevus. Moreover, the skin's reactions to intracutaneous injection or implantation of tumor material remains a promising prognostic indicator and a potential tool for cancer diagnosis. Some idea of cancer patients' prognosis can be obtained by studying their susceptibility or resistance to skin sensitization using a battery of skin-sensitizing allergens.

Diagnostic methods for the discovery of immunodeficiency, immunocompetence, or immunoincompetence include, as a simple, inexpensive step, skin testing with 2,4 dinitro-1-chlorobenzene (DNCB), toxoids, extracts of fungi (trichophytin or candicidin), streptokinase and streptodornase, mumps antigen, and so forth. This is a standard test of one mechanism of a patient's ability to resist diseases due to certain microorganisms, to viruses, and his capacity to reject tumor cells.

To cite another pertinent example, H. Sherwood Lawrence would not have been able to perform his superb work on the transfer factor without skin tests. The basis of his discoveries and analyses rested on the conversion from tuberculin skin-test negativity to tuberculin skin-test positivity when he transferred white cells from a tuberculin-positive individual to a tuberculin-negative one.

In still another modern but unrelated field, studies of the skin contribute a large share of new knowledge. For example, one way in which the miraculous drug aspirin acts as an anti-inflammatory agent is most readily shown by skin studies. Thus, Diane Schnyder of Miami, A. Kobza-Black, Malcolm Greaves, and coworkers in London, and others showed that skin inflammation (for example, caused by ultraviolet rays) can be mediated by release of certain prostaglandins inhibited by aspirin and by indomethacin.

Recent work confirmed and quantitated the role of the delayed type

hypersensitivity (today known as T-cell mediated hypersensitivity) in relation to immunity. The early work by Bruno Bloch and Massini and their followers demonstrated that delayed type trichophytin hypersensitivity of the skin was associated in some way with the production of a degree of immunity to skin infections by dermatophytes, another support for von Pirquet's basic concept. Von Pirquet coined the word allergy to indicate that specific, acquired hypersensitivity was intimately related to specific, acquired resistance or immunity and that both were due to analogous and often associated immunologic mechanisms. Investigators at Letterman Army Institute of Research used improved modern techniques to both confirm and expand the results of earlier workers on the relation of T-cell mediated hypersensitivity to resistance to skin infection.

Dr. Nigel Cruickshank of England provided our army investigators with a better trichophytin for skin testing, both more specific and more sensitive than the earlier cruder trichophytins. With modern methods we could count accurately and vary at will the number of fungal spores in the inoculum. By employing an occlusive dressing method of inoculation we could produce takes with predictable regularity. And these better techniques could be applied to large numbers of volunteers, kept under almost constant conditions and perfect control, and available for regular examinations. Added to these advantages was the important safety factor of being able to cure the experimental disease at will with griseofulvin. Using these improved methods, Henry Earl Jones, Jeffrey Reinhardt, Michael Rinaldi,[3] William A. Akers, and collaborators demonstrated that in men who had never had fungal skin infections and whose trichophytin skin test was negative for delayed hypersensitivity it took only one to six spores to produce an active, progressive infection in one half of those inoculated, i.e., the minimal infective dose over 50 was one to six spores (MID_{50} = 1 to 6 spores). In these trichophytin-negative, immunologic virgins the infection took 35 to 70 days to heal. In men with a history of previous fungal skin infection and who had a positive trichophytin skin test, it took 30 to 300 spores to produce active disease in half of those inoculated (MID_{50} = 30 to 300 spores). Moreover, it took only 21 days for the infections to heal in these men with previously established delayed skin hypersensitivity to trichophytin.

Possibilities to prevent and manage homograft rejection, many allergic skin diseases, infections, and many malignant tumors are almost limitless if physicians can at will prevent, reduce, or augment specific T-cell medi-

ated immunologic responses. Much work has this objective in mind. Studies by Medawar and his collaborators which prevented homograft rejection and work by Merrill Chase and by me and others which prevented skin sensitization by simple chemical allergens have been mentioned. A new and promising approach to the prevention of T-cell mediated hypersensitivity has been introduced by Baer and Rosenthal.[4] Verification and expansion of their investigations would offer potentially wide application in immunology and medicine. Baer and Rosenthal selected a chemical related to the strongly allergenic, strongly skin-sensitizing 2,4-dinitro-1-chlorobenzene. This chemical was 1,2-dichloro-4-nitrobenzene. The latter could neither sensitize nor elicit skin reactions in guinea pigs sensitized with the original dinitro compound. It was not an allergen, but one dose of this nonallergenic compound fed to guinea pigs 21 days before attempted sensitization inhibited sensitization of those animals by the strongly allergenic, 2,4-dinitro-1-chlorobenzene, a specific refractoriness to sensitization which apparently lasted for the rest of the guinea pigs' lives. I have called the nonsensitizing, immunogenic chemical relative of the sensitizing allergen an "allergenoid," a term analogous to the one used in relation to toxins, where a nontoxic immunogenic derivative of a toxin is called a toxoid.

The possibilities from allergenoids administered without risk of sensitization or eliciting reactions in the hypersensitive but which could prevent allergic sensitizations and responses are self-evident. They would be useful not only in allergic dermatoses but in innumerable other diseases based on T-cell mediated immunologic changes. Baer and Rosenthal fed this allergenoid to adult guinea pigs, obviously a more practical method for preventing hypersensitivity than if the material had to be administered to the fetus in utero (Medawar) and more practical than the administration of potentially sensitizing and damaging allergens, as in the experiments by Chase and me.

Turning to an example in which skin lesions produce severe systemic troubles, prickly heat is associated with obstruction of sweat ducts and pores, and it is followed by a period during which sweat cannot be delivered to the skin's surface from the blocked pores. This type of prickly heat and its subsequent anhidrosis were produced by our investigators (Wiley, Maibach, T. Griffin, and David Harris) at the Letterman Army Institute of Research.[5-7] We wrapped areas of the skin of normal volunteers with a closely fitting, occlusive dressing of Saran Wrap and exposed the

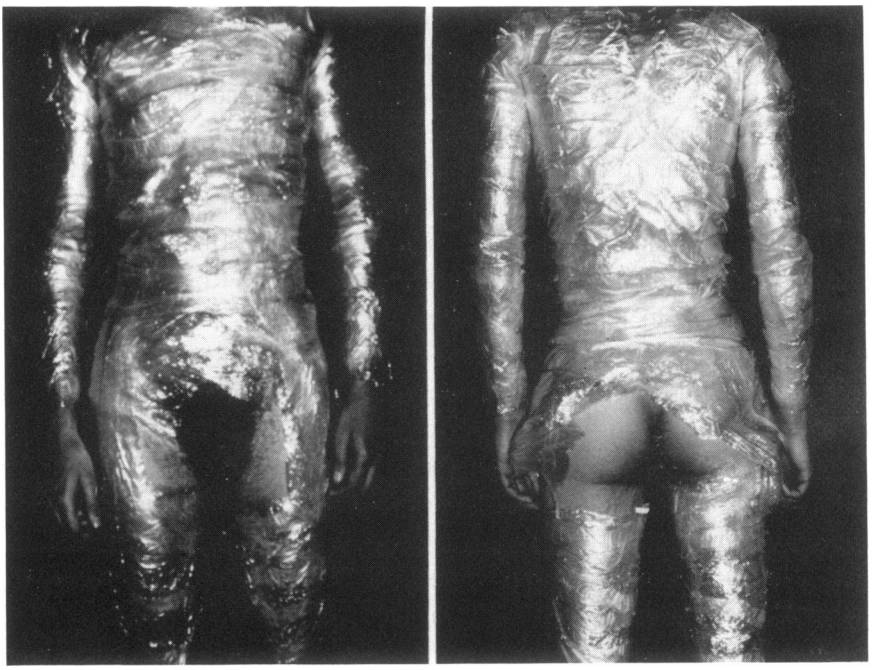

Fig. 4. Volunteer with Saran Wrap occlusive dressing over 60% of body surface. Reproduced by permission from Sulzberger, M. B. and Griffin, T. B.: Induced miliaria, postmiliarial hypohidrosis, and some potential sequelae, *Arch. Dermatol. 99:*145, 1969.

volunteers to a hot environment. In expansion of these studies, together with Robert Joy, Tommy Griffin, and Ralph Goldman, we selected 10 normal volunteers[8] and had them heat-acclimated at the Army Research Institute of Environmental Medicine in Natick, Mass. Six of these heat-acclimated men were wrapped over more than 60% of their skin surface with Saran Wrap (Figure 4). Wrappings were left in place for 96 hours. The other four men were not wrapped and served as controls. The 10 men were then placed upon a treadmill moving at 3½ miles per hour, in an environmental temperature of 135° F. at a relative humidity of 30%. Every one of the six men who had been wrapped and who had poral closures dropped out very shortly. Their core temperatures rose, they became confused, mentally obtunded, and several fainted (Figure 5). In contrast, the four control men who had not been wrapped and had no poral closures completed the exercise with ease.

The wrapped men had insignificant skin lesions not visible except to the careful observer who raised the environmental temperature and used a

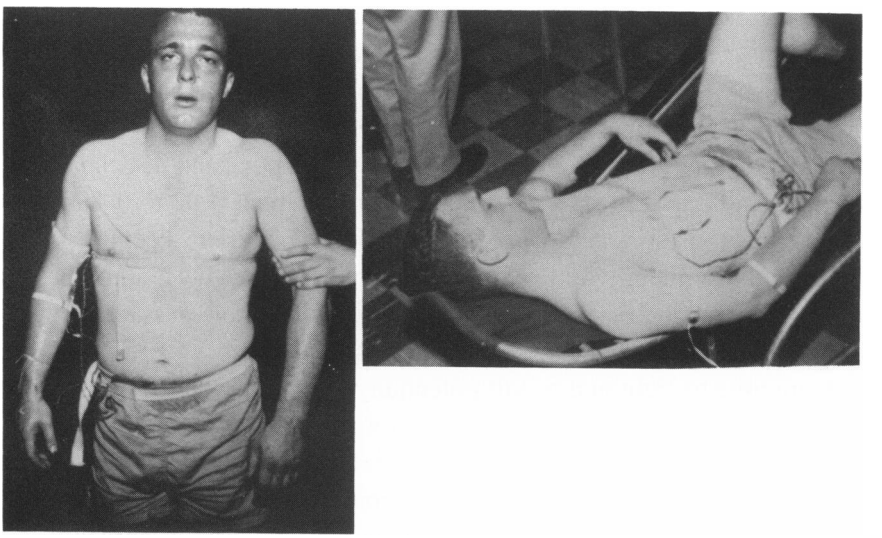

Fig. 5. One of the volunteers who (14 days after removal of occlusive dressing) first became exhausted and mentally confused and then fainted before being able to complete exercise on treadmill.

good light shining upon the skin at an angle. Even then their thousands of skin lesions looked like little goose pimples and were so inapparent that an ordinary physical examination would have failed to discover them. This syndrome, which Franz Herrmann and I called a form of the sweat-retention syndrome, closely resembled what is generally called heat exhaustion. It is therefore possible that cases diagnosed as heat exhaustion are primarily due to this unrecognized peripheral skin lesion. Workers in tropical climates, military personnel, workers in stokeholds, and workers in the deep mines of Africa, many of whom suffer heat exhaustion, may do so because of poral closures. The prevalence of pore closures, their pathogenesis and prevention, require much further study. Many of the people with this incapacitating somatic skin disease were accused of being malingerers, neurotics, and anything except sufferers from the anhidrotic sequelae of prickly heat. Occlusion of the sweat pores of only one third of the body surface is sufficient to make the individual unable to think or work efficiently in the heat.

Because of my fascination with this topic, I may be guilty of a lack of objectivity. But, in my opinion, a main function of the epidermis—I am tempted to say *the* main function—is to produce the horny layer. And I

suggest that studies of the horny layer, its abnormalities, mechanisms that produce these abnormalities, and how to prevent or counteract them hold great promise. Of course, the epidermis produces pigment, sweat, and sebum, but these products, important as they are, are less important than the horny layer itself, its composition, its properties, and its capacities. This thin, transparent, tough membrane averages about 0.02 to 0.1 mm. in thickness over most of the body surface. It is a barrier, keeping things which should remain within the body from getting out, and keeping potentially damaging materials from getting in. It controls passage of water and water vapor through the skin. It serves as a receptacle for materials which are able to fight and to kill potentially damaging microorganisms. It acts as a sunscreen. It forms a reservoir for a water-in-oil emulsion which keeps the surface of the skin pliable and healthy. This emulsion, by giving off or retaining water from within or from without, gives the skin its plasticity, beauty, and softness. In other words, the stratum corneum is a miraculously effective boundary between the human organism and its environment, and is a functioning tissue, not an inert envelope.

Study of what passes through the horny layer or emanates from the horny layer's surface is one of the most promising fields for dermatologic research. This field includes the skin's capacity to attract or to repel insects. Studies of this capacity have been going on at the Letterman Army Institute of Research and the University of California in San Francisco for many years. Insects are attracted to the human body by emanations mainly from the skin's surface, that is, from or through the horny layer.

Franz Herrmann and I showed that the horny layer constitutes a receptacle for sebum, sweat, and other substances. And that the horny layer forms a reservoir for many different agents, including applied medicaments, was beautifully demonstrated by R. Vickers of Great Britain and then elaborated by Stoughton in relation to topically applied corticosteroids. When a medicament is applied to the skin and produces its local biologic effect, even after several days, simply rubbing that area can again release medicament from the reservoir, help it to penetrate and reproduce its original biologic effect.

If insect repellants could be made to remain within the reservoir formed by the horny layer, they could keep insect vectors of the most damaging and killing diseases of mankind from penetrating and injecting their pathogenic microorganisms. Use of the horny layer and its reservoir to prolong the persistence of insect repellants would be an incalculable ad-

TABLE IV. ECTOMEMBRANOSES I ("Too Wet")

Intertrigos
Otitis externa
Perlèche
Dysidrosiform eruptions
Fungal infections (e.g., candidiasis, "athlete's foot," tinea cruris, erosio interdigitalis)
Maceration
Symmetrical lividity of the soles
Tropical acne (?)
Miliaria (most cases)
Sweat-retention syndrome
Urinary incontinence, drooling, draining sinus tracts
Infants' skins

Causes include: faulty horny layer, hyperhidrosis, tight and occlusive clothing and coverings, "wet work", high environmental humidity, immersion in water.

Reproduced by permission from Sulzberger, M. B.: The effects of heat and humidity on the human skin, *Arch. Environ. Health 11*:400-06, 1965.

vance, considering that the insect-borne diseases include such scourges as encephalitides, filariasis, hemorrhagic fevers, and malaria.[9] Malaria alone affects 200,000,000 people and causes 2,000,000 deaths every year.

Imperfections in the horny layer lead to many different diseases. A horny layer that holds too much water or too little water can initiate many skin infections and such other skin alterations as fissuring, chapping, and so forth (I. Blank). And recently Kligman, Plewig, and coworkers have shown that the increase in cohesion of the horny lameliae within the neck of the follicles is part of the originating mechanism in comedones and the cardinal lesions of acne vulgaris.

And I must not leave the reservoir of the stratum corneum without mentioning its function in the circulation and holding of lipids, which, when exposed to ultraviolet light, form the Vitamin D essential for the maintenance of health.

I would like to close with a rather amusing but, I believe, nonetheless extremely important observation, which came to my attention recently through an article in *The New York Times* of January 29, 1977. Anything which can alter the horny layer's capacity to retain water or lose water can be very significant in the management and prevention of skin diseases. Dr. Seamus O'Riain of Dublin[10] had a patient, a four-year-old boy, who had

TABLE V. ECTOMEMBRANOSES 2 ("Too Dry")*

Ichthyosis, ichthyosiform erythrodermas
Congenital ectodermal defects of anhidrotic type
Keratosis pilaris
Phrynodèrmas (xerosis)
Asteatosis (inborn and acquired)
Exfoliative erythrodermas
Chapping and fissuring
Atopic dermatitis (most cases)
Miliaria (a minority of cases)
Sweat retention syndrome (in desert)
Actinic dermatitis
Radiodermatitis
Aging

*Can be associated with infections, e.g., Trichophyton purpureum and Candida infections.
Causes include: genetic anomalies, faulty horny layer, dietary and vitamin deficiencies, atopy, drug eruptions, aging, "wet work."
Reproduced by permission from Sulzberger, M.B.: The effects of heat and humidity on the human skin. *Arch. Environ. Health 11*:400-06, 1965.

cut and severed the sensory nerves of two of his fingers. His mother, an acute observer, saw that when her son's hand was immersed in warm water for a while, the horny layer of the fingers and palms became white and swollen, as is normal, except for the two fingers whose nerves had been severed. In these, the horny layer did not swell, get white, or shrivel, but remained smooth. She reported this to Dr. O'Riain, who verified it by immersing the boy's hand in warm water. O'Riain repeated this at periodic intervals and noted that when the nerves recovered and the sensation in these two fingers returned, the normal swelling of the horny layer again took place upon warm water immersion. Dr. O'Riain then studied a series of cases and found that the phenomenon was indeed a general one. One could follow sensory nerve damage and sensory nerve repair by simply immersing the hand in warm water for 30 minutes, and seeing whether the horny layer did or did not swell.

Having no idea that the horny layer's ability to take up and retain water could be influenced by sensory nerves, I was not only interested but anxious to hear of a confirmation of Dr. O'Riain's findings. Recently, Dr. John Kasch, a resident in dermatology at Stanford University Medical School, has written me that he had confirmed Dr. O'Riain's findings, both in traumatic nerve injuries and in the sensory disturbance of the nerves due to leprosy. Here indeed is a fertile field for further dermatologic studies

which may have bearing upon a host of diseases, ranging all the way from ordinary chapping through the numerous diseases which are caused by the horny layer being too dry or too wet. Some years ago I gave some of these diseases the name of the ectomembranoses and divided them into two classes: ectomembranoses, too wet, and ectomembranoses, too dry (Tables IV and V).[11]

I have tried to show that the skin remains the sovereign organ for scientific investigations. Nowhere else can so many questions of fundamental importance be answered so precisely and so readily as in studies of this accessible and relatively safely manipulated tissue.

As our government becomes more and more responsible for treating patients and preventing disease and disability, the impact of skin diseases upon the public health and public purse will become more and more apparent to administrators, law-makers, and members of the government, as well as to the public. When this becomes inescapably and widely apparent, dermatology will again come into its own and will receive its merited facilities and funds. This renaissance in dermatology's prestige and support will see the skin hold its place as tomorrow's organ of discovery.

REFERENCES

1. Johnson, M-L. and Roberts, J.: *Prevalence of Dermatologic Disease Among Persons One to 74 Years of Age: United States.* Advanced Data from Vital and Health Statistics of the National Center for Health Statistics; U.S. Department of Health, Education, and Welfare, No. 4, January 26, 1977.
2. Sulzberger, M.B.: Ausführungen über einige dermatologische Beiträge zur kosmetik und zur wissenschaftlichen Medizin. *Hautarzt 15:*3, 1964.
3. Jones, H. E., Reinhardt, J. H., and Rinaldi, M. G.: Acquired immunity to dermatophytes. *Arch. Derm. 109:*840, 1974.
4. Baer, R. L. and Rosenthal, S. A.: Induction of cross-tolerance for contact sensitivity by a non-immunogenic chemical. *J. Immunol. 108:*706, 1972.
5. Sulzberger, M. B., Griffin, T. B., and Wiley, H. S.: Miliaria and anhidrosis. (1) Experimental production in volunteers. *Dermatologica 135:*414, 1967.
6. Sulzberger, M. B. Griffin, T. B., and Maibach, H. I.: Miliaria and anhidrosis. (2) The relationships between miliaria and anhidrosis in man. *J. Invest. Dermatol. 49:*379, 1967.
7. Sulzberger, M. B. and Harris, D. R.: Miliaria and anhidrosis. (3) Multiple small patches and the effects of different periods of occlusions. *Arch. Dermatol. 105:*845, 1972.
8. Sulzberger, M. B. and Griffin, T. B., Induced miliaria, postmiliarial hypohidrosis, and some potential sequelae. *Arch. Dermatol. 99:*145, 1969.
9. Hiatt, H.: Eradicating tropical diseases. *The New York Times.* March 23, 1977.
10. O'Riain, S.: New and simple test of nerve function in hand. *Br. Med. J. 3:*615, 1973.
11. Sulzberger, M. B.: The effects of heat and humidity on the human skin. *Arch. Environ. Health 11:*400, 1965.